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HFA-305, Room 1061
Food and Drug Administration
Division of Management Systems and Policy
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RE: Docket No. **99D-2873**

Medtronic is pleased to provide comments on the CDRH draft "Guidance for Industry and FDA Reviewers on Evidence Models for the Least Burdensome Means to Market." Medtronic is the worlds largest manufacturer of implantable medical devices. Our implantable devices provide therapy for a wide range of medical conditions including cardiac arrhythmias, coronary artery disease, chronic pain, movement disorders, spinal degeneration, and urinary incontinence. Our implantable devices are generally subject to the highest level of regulatory scrutiny including marketing via the PMA pathway. As a result, Medtronic has a very strong interest in CDRH's implementation of the least burdensome provision of FDAMA.

Medtronic believes that regulatory market approvals need to be based on good science. But given the spectrum of medical devices, there is not a single approach to the generation of scientific data which applies to all devices. Approval requirements need to be tailored to the safety and effectiveness or substantial equivalence issues posed by each specific device. We believe Congress understood this in the development of the least burdensome provision of FDAMA. Congress was also clearly aware of the inordinate delays in device market approvals and clearances in the early 1990's. The least burdensome provision, we believe, reflects Congressional intent that CDRH balance risks and benefits in device approvals and clearances to avoid over regulation and ensure the timely availability of new safe and effective medical devices to the American public.

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Medtronic welcomes the CDRH draft guidance as the first step in developing a process for determination of least burdensome requirements. We strongly agree that a process approach is needed to reach the least burdensome determination. It can help industry and ODE reviewers in their respective consideration of the appropriate level of data necessary to support market approval or clearance. More importantly, it can help focus early discussions between ODE and the device sponsor regardless of whether there are informal or formal determination or agreement meetings under FDAMA.

As a major manufacturer of PMA devices, Medtronic is deeply concerned about the process for least burdensome determination of clinical data requirements. It must be a central focus of the least burdensome guidance. But by considering only clinical requirements, the applicability of the draft guidance is severely limited. Rather than finalize such limited guidance, Medtronic strongly urges CDRH to work directly with industry to develop comprehensive guidance that will apply to all devices.

Medtronic endorses the comments of the Least Burdensome Task Force (Attachment 1). The Task Force was comprised of members representing a number of trade organizations and a broad spectrum of the medical device industry. Medtronic was a member of that Task Force.

Rather than reiterate the specifics of the Task Force comments, Medtronic comments will focus on specific topics where we believe our experience provides additional insight.

Industry versus the CDRH Model

The draft includes the industry model and specifically solicits comments on , the industry model. FDA inappropriately refers to this as the HIMA model. The Least Burdensome Task Force, which represents the membership of several industry trade associations, prepared it. While the agency's draft guidance chose not to adopt the industry model, CDRH recognition of the industry effort is noteworthy and greatly appreciated.

Both models share certain basic similarities. Both are process models. The CDRH model uses a question format to help lead to the determination of least burdensome requirements. The industry model uses a series of positive and negative examples for the same purpose. Both focus initially on the determination of whether clinical data are needed to support market approval and clearance. Once a determination has been made that clinical data are required, both focus on the hierarchy of valid scientific evidence in 21 CFR 860.7. But at this point their use of the hierarchy differs markedly.

The industry model starts at the lowest level of the hierarchy of valid scientific evidence and would work upwards to determine the least burdensome means. By contrast, the agency model starts at the top of the hierarchy by posing the question: "is a randomized controlled trial (RCT) the least burdensome means to provide reasonable assurance that the subject device is safe and effective, to establish substantial equivalence to a predicate.. . ."

Under ideal circumstances, either model could lead to the least burdensome means. However, in the real world, Medtronic believes that the industry model offers the most practical and reliable method to reach the least burdensome means and avoid over regulation. While we understand, in part, CDRH's desire to promote the use of RCTs, they have offered no evidence that devices approved without RCTs are not safe and effective or are in some way inferior to those devices that used RCTs. Thus we strongly urge CDRH to adopt the basic concept of the industry model. The basis for our conclusion is outlined below.

While endorsing the industry model, we recognize that it, like the CDRH model, is incomplete. Neither provides enough structure to the process to ensure reliable, consistent determination of the least burdensome means. The examples alone are not sufficient in the industry model. Similarly the agency model's two-question flow chart even with the points to consider is not detailed enough. Medtronic believes that a comprehensive process flow chart is necessary which incorporates the appropriate questions and considerations directly into the determination process. The flow charts for determining when modifications to 510(k) and PMA devices require submission provide good models for the level of detail needed here. Without sufficient detail, the determination process will be too subjective and result in continual disputes between ODE reviewers and device sponsors. In developing the additional detail, it also makes sense to extend the model to ensure inclusion of all 510(k) devices and IVDs. We also strongly believe that the development of this comprehensive model requires direct collaboration between CDRH and industry.

The Need for CDRH-Industry Collaboration

The Least Burdensome Task Force has made a strong case in its comments on the need for direct collaboration between CDRH and industry to develop a comprehensive workable model for determination of least burdensome requirements. Medtronic strongly supports this view.

To date there has been limited communication – in the stakeholders' meeting and in the respective models – but no real collaboration. Unfortunately CDRH has been precluded (by FDA's top management directive) from direct collaboration with industry in the implementation of the FDAMA provisions. At the HIMA Submissions Workshop in July, however, Dr. Susan Alpert indicated CDRH's willingness to work with industry directly on the least burdensome implementation once the comment period on the draft guidance has closed. We trust that CDRH's position has not changed as a result of her departure. Medtronic is willing and ready to provide our support to a CDRH-industry team approach to developing the least burdensome guidance. We would also support the inclusion of representatives from the medical community in this process.

In our experience, the lack of collaboration often results in misunderstanding. A clear example is the belief expressed in the draft guidance regarding the industry model that "the practical impact of applying this approach would require that data that is lower on the hierarchy of valid scientific evidence be fully developed and reviewed before a decision could reliably be made to proceed to the next higher level."

It was neither the intent nor expectation of the Least Burdensome Task Force that this is how the industry model should be implemented. But with the lack of any direct discussion with the Least Burdensome Task Force during the period between submission of the industry proposal in March and release of the draft guidance in September, it is easy to understand how such misinterpretations can arise.

One of the hallmarks of CDRH since the early 1990's has been their willingness to work constructively and collaboratively with industry in the development of key regulations and guidances. Some examples of where such collaboration occurred include

- FDA-HIMA Working Group on the Quality Systems Regulation
- Quality System Inspections Reengineering Team
- Guidance on When Modifications to a 510(k) Devices Require a New 510(k).
- Guidance on When Modifications to a PMA Device Require a PMA-Supplement
- Product Development Protocol Reengineering Team

Medtronic representatives participated on each one of these CDRH-industry working groups. Our experience was uniformly positive. The direct communication resulted in a clear understanding of each other's views and concerns which in turn resulted in regulations and guidances that are clearer and more workable for both CDRH and industry.

RCTs are Not Least Burdensome

As indicated earlier, Medtronic has broad-ranging experience with PMA devices. Since January 1, 1997, current Medtronic businesses have obtained approval for 13 original PMAs and 142 PMA-Supplements. Over that same time period, ODE statistics indicate that ODE approved approximately 45 PMAs and 300 PMA-Supplements per year. These statistics suggest that Medtronic experience accounts for. close to ten percent of all PMA and PMA-Supplement approvals per year. This experience gives Medtronic a solid basis for commenting on the burden and role for RCT in device approvals.

The draft guidance advocates that RCTs are least burdensome from the standpoint of FDA review alone. However, it ignores the burden placed on sponsors, investigators, and patients to conduct RCTs. In determining least burdensome requirements, FDA must consider aspects of burden from development and evaluation through approval and clearance. Considering only FDA review will lead to greater use of RCTs than necessary. This is over regulation and not least burdensome.

Nevertheless, Medtronic believes there is a role for RCTs in device clinical trials. Breakthrough devices, those which provide major new therapeutic advances, are the strongest candidates for RCT. But RCTs are not appropriate for all breakthrough devices. One relevant example is for life-saving therapies where there is no satisfactory alternative. Medtronic has shared its experience with our Cardiomyoplasty device which was developed in the early 1980's to treat patients with heart failure. At that time, drugs were the standard therapy and could only alleviate symptoms. We started an RCT using drugs as the control. The study and the device were eventually abandoned because of recruitment problems associated with the RCT design. Patients who were randomized into the control arm dropped out of the study because the study offered them no hope. The Cardiomyoplasty device was one of the examples included and a more complete description is included here in Attachment 2.

Devices evolve incrementally and subsequent generations can generally use data from previous generations as historical controls minimizing the need for RCTs. Other circumstances where RCTs may be appropriate include those where it is necessary to find small differences from prior devices in order to establish safety and effectiveness where device endpoints are subjective or where a device sponsor wishes to develop certain comparative claims. In our experience, these circumstances are rare and that breakthrough devices are the primary source of RCTs.

We believe that in practice only a small percentage of approved IDEs incorporate RCTs. To support this view, we offer the following analysis.

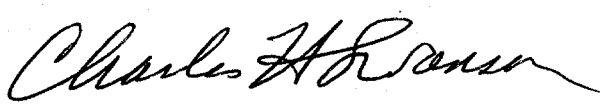
ODE approves 200 to 250 new IDEs per year. ODE also approves 40 to 50 original PMAs per year. This suggests that perhaps 20 to 25 percent of IDEs are associated with original PMAs. Breakthrough devices represent a subset of the original PMAs. RCTs for devices approved by PMA-Supplement are rare – we estimate less than 10%. As indicated above, Medtronic businesses have received approval for 13 original PMAs since January 1997. Attachment 3 is a listing of those PMAs. Six of the 13 PMA devices can be categorized as breakthrough devices. Four of the six involved RCTs although in one (Sofamor Danek Interfix Threaded Fusion Device) the RCT design was abandoned because of difficulties in patient recruitment. The remaining seven original PMAs involved technical advancements that ODE determined required a new PMA but are not breakthrough devices. Of these seven devices only one involved RCTs. Thus, in total, 5 of 13 or approximately 40% of Medtronic original PMAs involved RCTs. If our experience were indicative of other original PMAs, this would correlate with approximately 20 original PMAs involving RCTs. Even if one assumes that a comparable number of device approvals by PMA-Supplement involve RCTs, it is clear that IDEs involving RCTs , represents a distinct minority of IDEs approved annually. CDRH has access to IDE information which Medtronic does not and we encourage CDRH to carry out its own evaluation.

While CDRH has promoted the use of RCTs, they have offered no evidence that devices approved without RCTs are not safe and effective or are in some way inferior to those that used RCTs. Under these circumstances we believe it is clear that for the majority of devices – PMA or 510(k) requiring clinical data – RCTs will <u>not</u> be the least burdensome means to support market approval and clearance. Thus we believe that a least burdensome model that starts with RCTs is inherently inefficient and burdensome. Beyond that we are concerned that the CDRH model will lead to significant over regulation. It has the potential to establish a culture within ODE reviewers that RCTs are the gold standard and RCTs will be required when they are not needed. This was evident at ODE immediately following the issuance of the Temple report.

For all these reasons, we believe that the approach offered by the industry model offers a more effective and reliable means to reach a least burdensome determination.

Again, Medtronic appreciates the opportunity to comment on this draft guidance and we look forward to working with CDRH to develop comprehensive guidance on the least burdensome means for product approvals and clearance.

Sincerely,



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CC Dr. David Feigal, MD, FDA

Attachments (3)

ATTACHMENT 1

Comments of the HIMA Least Burdensome Task Force

HIMA
HEALTH INDUSTRY MANUFACTURERS ASSOCIATION

JAMES S BENSON
EXECUTIVE VICE PRESIDENT, TECHNOLOGY AND REGULATORY AFFAIRS

November 24, 1999

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docker No. 99D-2873

Dear Sir or Madam:

The Least Burdensome Task Force (the Task Force), a coalition of members from the medical device industry, is pleased to provide the following comments on the Food and Drug Administration's (FDA) "*Draft Guidance on Evidence Models for the Least Burdensome Means to Market.*" The Task Force is comprised of representatives from the following organizations: Health Industry Manufacturers Association (HIMA), Medical Device Manufacturers Association (MDMA), National Electronic Manufacturers Association (NEMA), Association of Medical Diagnostics Manufacturers (AMDM), Joint Council of Immunohistochemical Stain Manufacturers (JCIM), Massachusetts Medical Device Industry Council (MassMEDIC), Medical Alley, Indiana Medical Device Manufacturers Council (IMDMC), and the Cook Group.

The "Least Burdensome" provision, Section 205 of the Food and Drug Administration Modernization Act'of 1997 (FDAMA), is a major provision of FDAMA designed to reduce the burden and time required to bring new safe and effective medical devices to patients: in the United Stares. The intent of FDAMA is to foster collaboration between the Center for Devices and Radiological Health (CDRH) and device sponsors to determine the least burdens&me means of product approval and market introduction. Industry's commitment is reflected in our participation in FDA'S "least burdensome" stakeholders meeting and in our development of the early proposal for least burdensome determinations. FDA's inclusion of the industry proposal is recognition of that commitment. The Task Force also welcomes the FDA's draft guidance as an important step forward and acknowledges the agency effort that this reprcscnrs. We strongly agree that the guidance needs to take a process approach to the determination of least burdensome requirements- This is critical to develop common understanding between industry and CDRH as well as consistency in implementation across Office of Device Evaluation (ODE) divisions. Both the FDA and Task Force proposals are process-based albeit with different

approaches. The Task *Force* also agrees with the "General Principles" outlined in the draft guidance. It is critical that they be translated directly into the least burdensome determination process. Finally, we agree with FDA that its draft guidance is a first step in that it focuses only on clinical data needs and specifically excludes in vitro diagnostics (IVDs). Direct collaboration between CDRH and industry is needed to develop a comprehensive "least burdensome" guidance.

The Task Force believes that a comprehensive "least burdensome" guidance would benefit greatly from a joint effort and thus recommends that CDRH form a "least burdensome" working group, consisting of industry, CDRH and other appropriate participants to revise the published draft guidance document. In the past, there have been many instances of industry/agency collaboration and dialogue that have resulted in strong programs such as the Product Development Protocol reengineering initiative, and the PMA Supplement and 510(k) modifications guidance documents. As the Task Force noted in its letter dated November IS, 1999 to Dr. David Feigal, the Task Force is looking forward to the meeting with the agency to discuss these comments and to explore ways in which industry and the agency can work together to revise the guidance document.

In recent testimony before the Senate Committee on Health, Education, Labor, and Pensions (HELP) on October 21, 1999, Pamela Bailey, president of HIMA, stressed the need to restore industry/agency discussion prior to issuing guidance documents or shaping programs'; The need for industry/agency interaction in the area of "least burdensome" is of the utmost importance. We believe that the lack of industry/agency dialogue resulted in FDA's misunderstanding and mischaracterization of the least burdensome proposal submitted by the Task Force. Contrary to being the arduous process described by FDA, the industry proposal closely tracks Congress's intent in enacting the FDAMA provisions requiring consideration of&e "least burdensome" means of supporting device approvals or clearances. Through comments and collaboration with FDA, we hope to avoid misunderstandings and constructively contribute to making Congress's FDAMA approach work.

The Task Force welcomes the opportunity to provide comments on the draft guidance. Our comments are directed at identifying the key issues for further discussion and resolution and we look forward to collaborating with FDA to develop comprehensive guidance.

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[1] Testimony of Pamela G. Bailey. Health Industry Manufacturers Association, Hearing on Implementation of the Food and Drug Administration Modernization Act of 1997 before the Senate Committee on Health, Labor, Education and Pensions, October 21, 1999.

Definition of Least burdensome and a Process for Implementation

To achieve the intent of FDAMA in the implementation of the least burdensome provision, the Task Force recommends the need for both a functional definition and a process for least burdensome. We propose to define least burdensome as:

> Determining the most appropriate level of (1) valid scientific evidence for PMA devices to determine reasonable assurance of device effectiveness or (2) information necessary to demonstrate substantial equivalence for S 1 0(k) devices. The process for determining this most appropriate level should confine submission requirements to essential issues to support approvals or clearances, eliminate inappropriate and unnecessary testing and FDA reviews, and provide an opportunity for prompt resolution of scientific differences between FDA and device sponsors thereby ensuring the development and market approval and clearance of new, beneficial devices without delays attributable to over-regulation.

Further, we believe that the least burdensome concept is best implemented by a process that will produce understanding between FDA and industry on the level of appropriate data needed to establish a reasonable assurance of safety and effectiveness or substantial equivalence. Because data requirements are specific to each type of device, the process must include an effective and objective methodology for determining what data arc essential, for eliminating nonessential data requirements and for promptly resolving disputes. In other words, obtaining 3 least burdensome result for a specific device process is best achieved through a well-defined and interactive process between FDA reviewers and device manufacturers.

To be effective, the process must include steps to:

- identify the issues or questions related to safety and effectiveness or substantial equivaicncc,
- discriminate bctwccn essential and nonessential issues on the basis of scientifically sound rationale,
- eliminate nonessential data requirements,
- establish practical methods for determining essential data, and
- resolve disputes between FDA and industry regarding a least burdensome determination through a fair, equitable, and efficient process.

For PMAs, least burdensome is defined primarily by clinical data which are valid scientific evidence within the meaning of 21 CFR 860.7(c)(2). While this regulation refers to clinical

trials, for PMA devices, data from laboratory (chemical, electrical, mechanical) or pre-clinical animal studies are also implicitly within the scope of the least burdensome process because such data serve to limit the clinical testing requirement.

Requirements for valid scientific evidence should be confined to answering only those questions that are pertinent and essential. Focused studies are more likely to yield definitive results. In many cases, studies are expanded beyond the essential issues with the misconception that they are more comprehensive when, in fact, they are less focused and result is less definitive data. For example, a well-defined laboratory or animal study may substantially answer an effectiveness issue, thus limiting the scope and kind of clinical study that would be necessary to demonstrate device effectiveness, or completely eliminating the need for a clinical trial.

The process should recognize the importance of eliminating non-essential efforts. The unnecessary consumption of resources and time for non-essential testing detracts from and diverts resources from more productive efforts and often leads to uncertainty and delays in the review process. Therefore, it is important to acknowledge that some tests are nonessential. Nonessential tests may include laboratory, animal or clinical testing involving outdated methods, previously-answered questions, curiosity questions, testing requirements and requests due to reviewer inexperience or lack of specific knowledge, impractical methods and methods beyond those required to obtain or adequately analyze the data.

The most likely process to succeed is one in which data requirements are commonly agreed to by industry and FDA and are listed as such. When industry and FDA disagree about data requirements, there must be a formal process to require both FDA and industry to document scientifically sound justifications and counter-arguments. Documentation should be sufficient to allow, an independent party to make judgments based on the scientific merits. Further, all existing product-specific guidance documents should be reviewed by FDA to determine whether they comply with the least burdensome concept. Additionally, future FDA guidance documents including data requirements should be developed cooperatively and with least burdensome concepts in mind. By establishing mutually agreed upon data rcquiremenrs, the variability created by the range of industry and reviewer knowledge and experience is minimized.

The development of a process for establishing the least burdensome methods has several advantages while not compromising the scientific rigor of premarket testing. It focuses testing and review efforts to address essential issues and minimizes workload for all parties. Industry and FDA resources can be better directed for a more controlled review process, with the benefits of improving global competitiveness and reducing the delays in patients' access to new beneficial medical technology.

Scope of guidance

The scope of the industry proposal covers all devices, consistent with the least burdensome provisions of FDAMA. The proposal also covers all types of devices regulated through the 5 10(k) and PMA processes, including TVD devices. FDA appears to understand the Food Drug and Cosmetic Act (the Act), yet failed to draft its guidance in parallel with the scope of the law. Although FDA states on page 2 in the section entitled "Scope of this guidance," the intent to "establish a general approach for applying least burdensome provisions that will be applicable to any device application," CDRH describes the guidance as limited to clinical data and excludes IVDs because of purportedly "unique clinical data needs associated with establishing IVD performance." The Task Force does not accept the argument for the IVD exclusion. There is uniqueness in other types of devices, and therefore, IVDs should not be singled out, particularly if the broad concepts of least burdensome are adopted

FDAMA's "least burdensome" provision applies to all devices, does not distinguish between types of devices, and is not limited to PMAs or to 5 10(k) submissions requiring clinical data. We believe that this very limited scope greatly detracts from the value of the guidance document to FDA reviewers and industry and fails to meet the spirit of FDAMA's provisions for "least burdensome." On page 5, first paragraph, CDRH acknowledges that for 5 I O(k) submissions, 'hew clinical data are not required in most of these circumstances." As such the number of devices/manufacturers having access to "least burdensome" will be quite small. Per the ODE Annual Report, Fiscal Year 1998, (55) PMA submissions were received compared to (4,623) 5 1 O(k) submissions, with only approximately 10% of 5 1 O(k) submissions requiring clinical data.

We recommend that, before implementation, the draft guidance be revised to include all types and classes of products, including IVDs, as well as consider "least burdensome" for all types of data. By increasing the scope in this way, *all* device submissions would have access to "least burdensome." Most 5 1 O(k) submission reviews would benefit if 5 10(k) submission information were limited to that information necessary to a substantial equivalence determination. IVD submissions would be considered under the same policies as other medical device submissions. To address the agency's concern that a broader scope would be unwieldy. we believe that developing a decision tree with textual guidance like that used to develop the guidance "When to Submit a 51 O(k)" would be an effective means to make the process work. We are prepared to assist CDRH as part of an industry/agency least burdensome task force in achieving this goal.

Arc Randomized Controlled Trials Least Burdensome?

In FDA's model, the second consideration for determining least burdensome clearly reflects the agency's bias toward Randomized Controlled Trials (RCTs). However. the suggestion that RCTs

arc least burdensome warrants further scrutiny. FDA states, "stakeholders have tended to focus concerns regarding the least burdensome decision related to the need for an RCT because they have assumed that an RCT will be more costly in terms of time and money." Industry's concern is stated correctly and the industry proposal included clear examples where RCTs are indeed more burdensome. FDA maintains that RCTs are not always more costly in time and money but offered *no* data *or* examples in support of this view,

Clearly there are some devices for which RCTs arc least burdensome. But the Task Force believes that these represent only a small percentage of devices that require clinical data to support safety and effectiveness or substantial equivalence.

RCTs are the paradigm for determining drug safety and efficacy. This is appropriate because each molecular entity is a new drug, the interaction of an active ingredient with different inactive ingredients may vary drug effectiveness, and drugs generally act systemically. Their effects – positive and negative – are often subtle.

Fundamental differences between drugs and devices limit the need for RCTs for device studies and therefore make the requirement for RCTs overly burdensome. Consider:

- Device action is generally more localized and specific and its clinical effects more readily apparent.
- One of the rationales for RCTs in drugs is to eliminate the placebo effect. For many devices, particularly implants and others involving surgical procedures, there is little or no placebo effect.
- Devices evolve over time through a series of incremental improvements. This means that historical data very often exist which provide a valid control.
- Device evolution also means that very often the issues of safety and tffectiveness or substantial equivalence are focused on incremental features rather than the device as a whole, thus limiting the need for clinical data when bench data is fully adequate to address the change.

FDA indicates that RCTs are the easiest for FDA to review. This is most evident in the agency's assessment of the industry least burdensome model. WC strongly disagree with that assessment. For the majority of devices requiring clinical data, RCTs are not least burdensome. Guidance structured by the industry proposal provides 3 simple, direct process for FDA and the device

sponsor to jointly identify the most appropriate level of valid scientific evidence and the least burdensome approach. Once this is done, FDA review should be straightforward.

Comparison of FDA's Least Burdensome Model with Industry's Least Burdensome Model

We believe that the industry model is consistent with congressional intent for the least burdensome provision because it is inclusive of all types of devices, e.g., IVDs, and it applies to both PMA and 5 I O(k) submissions. Additionally, the industry model defines a process that begins with the base of the hierarchy of valid scientific evidence while the FDA model begins its approach with RCTs (the very top of the hierarchy) and does not consider the other types of valid scientific evidence on the hierarchy. The Task Force strongly believes that its approach is more appropriate for the following reasons.

- The FDA model starts with the premise that the RCT is best and is least burdensome. This directly conflicts with congressional intent. Congress enacted the least burdensome provision because of concern that FDA'S long approval and clearance times were unnecessarily and unreasonably delaying the availability of new improved medical devices. Part of that is directly attributable to CDRH's efforts following the Temple Report to implement a drug model for device evaluation with its attendant emphasis on RCTs. Because of the differences in the nature of development, mode of action, etc, the need for RCTs to evaluate safety and effectiveness is far less for devices than for drugs. Unnecessary demands for randomized controlled trials add excessive burden to the product life cycle.

- The FDA model also requires proof by the device sponsor that any alternative is better and less burdensome. No matter how good the process is for decision making, this model includes bias that will inevitably lead to more RCTs than necessary and more rather than less burden. WC believe the industry model will more likely lead to the determination of the appropriate level of scientific evidence necessary to support market approval.

- FDA's perspective of least burdensome is limited to its own role-i.e., in the review of device submission data. We believe congressional intent in mandating least burdensome was to minimize the burden on all parties (FDA, patients. clinical investigators and industry) and speed the time to market which also means reducing rhe duration of development and clinical cycle times. FDA's perspective will, without question, add time, cost, and burden to the investigation of devices. WC also reject the notion that RCTs arc themselves less burdensome for FDA to review. The appropriate level of scientific evidence to the device in question should require the least time and effort for FDA review and this will bc achieved more readily through the industry model.

- The industry *model* better addresses the spectrum of device clinical trials. The role for RCTs may he more appropriate to new breakthrough devices and therapies (i.e. those that require a first PMA), although even this statement is a generalization that is limited by numerous examples. In fact, breakthrough devices represen t a minority of device clinical trials. For most devices subject to marketing via 51 O(k) and for many second and third generation PMA devices, there are specific focused issues that require clinical data to support market approval. For these devices the appropriate level of valid scientific evidence is below RCTs on the valid scientific evidence hierarchy.

Finally, we believe that FDA has misinterpreted the industry model by implying that each level. of the hierarchy represents a submission of data that must be reviewed by FDA, thereby adding delays. We believe that the industry model, like FDA's, is a process model. The industry model uses examples to help determine the appropriate level. Although the FDA model uses 3 series of questions, it does not provide a well-defined structure that would Predictably allow one to reach a correct least burdensome decision. We believe that a flowchart of questions and examples could be developed to further strengthen the industry model. We propose that this be done in collaboration with FDA. As a final note, FDA's criticism of the purportedly arduousness of the industry approach, if applied to the agency's approach, would lead to the same criticism.

Consideration of Least Burdensome in Determination Meetings

Section 205 of FDAMA includes both the least burdensome provision and the provision for an early determination meeting with FDA. The purpose of the determination meeting is for FDA to specify the type of valid scientific evidence necessary to support PMA approval for the device in question. Clearly congressional intent is that this determination must bc made in the context of the least burdensome requirement. To date, FDA has gone out of its way to discourage determination meetings by implying none too subtly that determinations from such meetings would not bc least burdensome- For example, shortly after FDAMA passage, Dr. Bruce Burlington stated that FDA's default position would be to require RCTs. This attitude has not changed as reflected by Dr. Susan Alpert's comments at the most recent RAPS conference as quoted in the October 11, 1999 issue of the Gray Sheet. Dr. Alpert recommended sponsors pursue non-binding meetings in lieu of a binding determination meeting saying, "you can have [a determination meeting], but we think that gives [FDA] an awful lot of latitude to decide the terms of the binding agreement." If FDA was committed to implementing the least burdensome approach, the agency would use determination meetings as a way of putting "meat on the bones" of the least burdensome concept and, therefore encourage and not discourage such meetings. Moreover, the industry "bottom up" model provides a better, more harmonious means of

consulting in a determination meeting in comparison to a meeting focused on overcoming FDA's RCT presumption.

Least Burdensome: 510(k) vs. PMA Determinations

The draft guidance clearly applies to products cleared by 5 1 0(k)s and approved by PMAs where clinical data are required. The FDA's proposal fails to consider the bulk of 5 10(k)s that do not require clinical data to resolve technological differences. Also, we believe the draft guidance fails to consider another aspect of 5 10(k)s and PMAs that should involve a least burdensome consideration. Specifically, FDA's guidance should consider whether changes in technology, indications, etc., associated with a device initially cleared by 5 10(k) should be marketed via 3 5 1 O(k) or PMA. The FDA'S presumptive position should be for the agency to clear these products by 5 IO(k). Data requirements, FDA and sponsor resource requirements, and regulatory cycle times increase substantially when a device goes from 510(k) to PMA. This result would not be a least burdensome undertaking. A good example of this is digital mammography systems. Current technology is marketed via 5 10(k) but FDA appears ready to require a PMA for digital mammography. Tn the October 4, 1999 issues of the Gray Shea, Dr. Feigal is quoted as saying "although it sounds paradoxical, a PMA is something that may be less burdensome than a 5 10(k) [for digital mammography] (emphasis added)." If predicate technology can be adequately regulated via 5 1 O(k), there is little or no additional public health benefit that would justify the additional burden of the PMA process.

When considering whether or not to place a device onto a PMA track, FDA should aggressively use risk-based classification under section 513(f)(2) of the Act to avoid over-regulation, consistent with FDAMA's least burdensome philosophy. By assessing risk before requiring 3 PMA, FDA can avoid large burdens to itself and industry when 3 device could be regulated successfully as a class II or I device. This approach is especially sensible when FDA has extensive experience with devices that arc PMA candidates because of changes in indications of use. By virtue of its experience, FDA can evaluate such a device's likelihood for harm in the context of a new indication. Depending on the significance of the new indication, and FDA's experience with a device, a reasonable risk-based determination can bc made, thus providing FDA with the opportunity to avoid unnecessary PMAs.

Premarket Notification

FDA's proposed guidance fails to address the breadth and scope of the statute in the development of least burdensome requirements for all devices and particularly those subject to 5 1 O(k) clearance. An effective least burdensome guidance document must also address other issues that are not exclusive to premarket submissions for which clinical data are required. As acknowledged in the FDA draft guidance, very few 51 O(k) submissions will require clinical data

to demonstrate substantial equivalence. The need, therefore, exists to develop least burdensome criteria that do not focus primarily on clinical data requirements.

The need for non-clinical data in a 5 1 O(k) will vary depending on the type of device and experience with its use. For many products non-clinical data (biocompatibility, electromagnetic compatibility, internal results from design verification and validation) are sufficient to satisfy substantial equivalence determination and support the clearance of the device. For 51O(k) products. it should be a very rare circumstance when manufacturing data and other information more appropriate for a PMA submission are required in a 5 10(k). Unless, for example, there are issues unique to the manufacture of a particular device subject to 5 1 O(k) requirements, these types of issues should be left to FDA field inspection and should not be part of ODE review.

For those very few 5 1 O(k) submissions that do need clinical data to demonstrate substantial equivalence, it is important to note that the type of data and the clinical endpoints must be commensurate with 5 1 O(k) substantial equivalence requirements. For example, the type of data or endpoints needed as the basis of a substantial equivalence determination would nor address clinical utility. We recommend that a revised guidance clearly state the difference in type of clinical data and endpoints needed for a 5 10(k) submission as compared to a PMA submission

Guidance needs to consider device risk in determining what data – clinical or preclinical—are needed to support a substantial equivalence decision. 510(k) devices inherently pose a lesser risk than PMA devices. The gradation in risk in the 510(k) device population also needs to be addressed. The Task Force recommends that FDA and industry work together to develop comprehensive guidance rather than one with such limited applicability- .

Prcmarket Approval and 510(k)s with clinicals

Role of non-clinical data in clinical decisions and requirements

The language of the Act as modified under FDAMA indicates that clinical studies shall be required for PMA approval only when "necessary", i.e., when there is not other sufficient valid scientific evidence TO support approval. Further, the extent of data required for approval must be considered in light of possible postmarket controls. This clearly demonstrates congressional intent that clinical studies be required only after due consideration of all reasonable alternatives, not as the starting point in the early discussions between FDA and the device sponsor including Determination Meetings provided under FDAMA. Thus, WC believe that non-clinical data must be considered first when evaluating the least burdensome means of demonstrating the safety and effectiveness of a Class III device. This approach is not only consistent with the language of FDAMA, but also consistent with the provisions of the *Quality* System (QS) Regulation Design Controls.

Question 1 in the FDA Draft Guidance states "Does available valid scientific evidence provide reasonable assurance that the subject device is safe and effective, or establish substantial equivalence to a predicate device, when used as indicated in the target population'? (emphasis added)." Valid scientific evidence is generally construed to reflect clinical data. The context of this question needs to consider the preclinical testing for the device at issue as well as any prior clinical testing in determining whether there *is* reasonable assurance that this device is safe and effective or substantially equivalent without additional clinical data.

While the FDA is correct in stating that industry is concerned with FDA's interpretation of least burdensome requirements as they relate to clinical trials, the FDA has misinterpreted industry's concern. The industry is concerned nor just with what type of clinical data are of least burden, but also with the burden imposed through the collection of clinical data when it is not really needed.

Break-through technology

Industry recognizes that the revolutionary device by its very nature will raise new technological questions. Thus, these are the devices where the probability is greatest that a clinical study may be appropriate. However, even breakthrough devices may not need or be suitable for a RCT.

FDA guidance needs to incorporate risk analysis consideration into the least burdensome determination process. The QS Regulation, combined with the growing acceptance of international quality system standards in the medical industry, has focused attention on risk analysis as a central tenet of design control. Under design control (21 CFR 820.30), the manufacturer is tasked with identifying the potential hazards associated with the new device, Following risk analysis, the type of design validation required is to be dercrmined based on the identified issues. Thus, the scientific questions associated with potential clinical hazards should be well defined via risk analysis prior to defining the design validation program, including any required clinical studies. We believe that the determination of the type of valid scientific evidence necessary to demonstrate effectiveness in a PMA must be finked to these design validation questions in order to be considered least burdensome. Further, the burden on the sponsor, clinicians and patient populations to generate the data, not just the ease of the subsequent review process, must be considcrrd in determining the most appropriate study design.

Early dialogue/consultation with FDA

In order to reach an optimal determination of the least burdensome, appropriate means of demonstrating safety and effectiveness, the manufacturer must be able to meet with representatives of the review division to assure a common understanding of the potential risks and benefits of the new technology. The industry is best suited to inform FDA about these break-

through technologies. Early discussions with the FDA using a comprehensive process model for a least burdensome determination can identify the necessary burden for establishing safety and effectiveness. FDA's assumption that multiple submissions would be required in the industry model as used represents a fundamental misunderstanding that can be resolved in the development of a comprehensive model. Early collaboration is essential for the mutual education and exchange of ideas that must occur for break-through technologies to be brought to market in an expeditious manner.

Safety & Electiveness

Following the initial dialogue, an open consultation between FDA and sponsors should continue to determine the most appropriate clinical means of addressing those questions raised by the risk analysis that cannot be addressed through non-clinical means. These discussions should continue under the auspices of the formal early collaboration meetings anticipated by the FDAMA provisions for determination and agreement meetings as the mechanisms for identifying the least burdensome means of establishing safety and effectiveness. Further, this consultation can and should be based on a comprehensive process model incorporating the hierarchical principles outlined in the industry proposal.

The examples in FDA's draft guidance suggest that innovators must pave the way with RCTs before less burdensome approaches to establishment of safety and effectiveness will be considered by FDA. This argument is flawed for several reasons. First, such trials are not always appropriate. There may be ethical considerations making randomization improper or logistical considerations impeding effective masking of the trial. The examples provided with the industry proposal include examples where RCTs were inappropriate. Second, the automatic assumption that RCTs should be considered first, as presented in the draft guidance, is a potential disincentive to innovation, as such trials are clearly not viewed as least burdensome by the device industry. The open consultation contemplated by FDAMA requires equal consideration to alternative forms of valid scientific evidence.

Pre-market vs. post-market studies

Whenever possible, postmarkct controls must be considered as an alternative or adjunct to preapproval trials. This is particularly important in the case of break-through devices where a satisfactory diagnostic or therapeutic alternative is not available or where a new device offers significant safety and effectiveness advantages. One can always ask that additional data be gathered to address a "suspicion" or long-term concern about a particular device. The concept of least burdensome requirements is one in which such concerns must bc deemed insufficient to delay approval. If the patient group being treated by the device is at significant risk from the lack of the treatment, the FDA should consider tie use of post-market studies in reducing the

pre-market burden. FDA supports the use of postmarkct studies as a means to reduce premarket testing and the least burdensome process model is the ideal way to incorporate its consideration. To date there has been little evidence that FDA has considered the pre- and postmarkct trade off in early discussions of market approval and clearance requirements.

Device evolution and least burdensome

Clinical rcauirements for device changes

Brcakthrough devices represent only a fraction of the agency's PMA workload. The remainder is comprised of devices reasonably known to the FDA and the medical community. These include many original PMAs, for example "me-too'," or pre-amendments devices for which ample historical data exist to address most, if not all, of the design validation issues. Where clinical data are needed, clinical studies can and should be focused on'specific issues and differences from previous devices.

The remainder of the PMA workload consists of PMA supplements. Design control can again play a role in determining if there is a need for clinical data for device modifications requiring PMA supplements. The QS Regulation requires the manufacturer to determine the potential impact of any proposed device modification via the risk analysis. Following risk analysis, the type and extent of design verification and/or validation required is based on the potential hazards associated with the device change.

Thus for evolutionary devices, the type of clinical data, if any, can easily bc determined through a comprehensive least burdensome process model as described above. It may well be that design verification or simulated use studies are sufficient to address the scientific questions raised via the risk analysis. Alternatively, the scientific literature may provide ample evidence that the modification (e.g., a materials change) will not impact safety or effectiveness. In cases where design validation requires clinical testing, an open-label study to confirm that any potential new risks remain within acccptable risk:benefit ratios may suffice. Even if a well-controlled study was deemed necessary for the parent device, a small, confirmatory study with historical controls may be sufficient to validate the continued safety and effectiveness of the device following modification.

Use of literature

As discussed above, scientific literature can and should be appropriately used to reduce the premarket burden on device manufacturers. Where well-documented case histories and reports of significant human experience are relevant to the product modification, these types of valid scientific evidence must be considered prior to requiring new clinical data. The Task Force

believes that a comprehensive model for least burdensome determinations incorporating risk analysis can identify conditions where the use of literature is acceptable.

Appropriate controls for clinical studies.

FDA's draft guidance sets RCTs as the initial point of consideration for any clinical trial design. Given the spectrum of devices and clinical issues, this one-size-fits-all approach is inappropriate and inherently burdensome. Industry is required to prove that something less is more appropriate which FDA reviewers are unlikely to accept. The industry proposal based on the tiered hierarchy of valid scientific evidence presents a more realistic and meaningful approach to address the spectrum of medical devices. FDA concerns, we believe, represent misunderstandings that can be addressed by providing more detail in the process model and we are prepared to work with FDA to achieve this.

In conclusion, we would like to reiterate the need for an interactive process in revising the draft guidance document and the willingness of the Task Force to participate in a "least burdensome" working group, consisting of industry, CDRH, and other appropriate participants to revise the guidance. Industry's Least Burdensome Task Force is very committed to working with the agency to accomplish the revision and would like to accept FDA's offer to meet after the conclusion of the official comment period. Again, we appreciate the opportunity to provide these comments.

Sincerely,

Jim Benson

James S. Benson
For the Industry Least Burdensome Task Force

ATTACHMENT 2

Cardiomyoplasty Device and Least Burdensome Requirements

Cardiomyonlasty Device and Least Burdensome Requirements

- The Cardiomyoplasty device was designed to treat patients with advanced heart failure including those eligible for heart transplants. Drug therapy can at best offer only temporary relief for these advanced-stage patients.

- Cardiomyoplasty involves wrapping the heart with a muscle from the back (latissimus dorsi) and stimulating that muscle in synchrony with the normal heart contractions to improve cardiac function. The device combines the electrical sensing characteristics for implantable cardiac pacemakers with the electrical stimulation characteristics from an implantable neurological stimulator.

- The Medtronic Cardiomyoplasty device received initial IDE approval in December 1988, for an initial single-center feasibility study. FDA required a three-phase study design to support market approval. Phase II, a multicenter, non-randomized study was approved in May 1991. Phase III, a randomized trial with approved drug therapy as the control, was approved in August 1994. Agreement on the protocol design for each phase was prolonged requiring a year or more.

- From the beginning, problems were encountered with the randomized design of the trial which greatly frustrated progress.

  ♦ Agreement on appropriate endpoints: Comparison based on patient survival would have required a very large trial with long-term follow-up. Intermediate or surrogate endpoints were sought which could identify patient benefits in a smaller study. Agreement on appropriate endpoints was difficult.

  ♦ Retaining patients in the control arm: This was a major problem with 50% of the control patients dropping out of the study initially. Patients often are interested in participating in the study initially because it offers them some hope. When randomized into the control arm, that hope is gone 'and there is little incentive for them to continue. We worked with FDA to develop a cross over option but its success was limited. To date, 10 control patients have crossed over while another 12 were either too sick or died before crossover could occur.

- ◆ During the study, it was noticed that a number of patients survived the implant procedure but ultimately died of sudden cardiac death. A second-generation device was developed which combined Cardiomyoplasty and cardioverter/defibrillator therapy. However, FDA has been reluctant to seriously consider this device until the safety and effectiveness of basic Cardiomyoplasty therapy was proven even though some investigational patients were already receiving ICDs. This change illustrated the evolutionary nature of device technology as well as how the regulatory system can frustrate and delay the availability of device improvements.

- These factors have all contributed to a lack of progress in this study and ultimately to Medtronic's decision to terminate the study and efforts to seek market approval. After four years, only 103 patients out of the required 400 have been enrolled in Phase III. It is estimated that completion of the trial would require another four to five years.

- Termination of the study is unfortunate because the results have been encouraging. Our medical experts agree that the study design was scientifically sound. But the randomized trial which essentially required demonstration that the Cardiomyoplasty device was a standard of medical care posed an overly burdensome requirement that could not be overcome.

ATTACHMENT 3

Original PMA Approvals by Medtronic . Businesses since **1997**

Original PMA Approvals by Medtronic Business Since January 1997[1]

DEVICE	APPROVAL	BREAKTHROUGH?	RCT DESIGN?
1. Hancock II Prosthetic Heart Valve	9/28/99	No	No, OPCs used [2]
2. AneuRx Stent Graft for Abdominal Aortic Aneurysms	9/28/99	Yes	No, surgical controls were completed at each center prior to enrolling stent graft patients
3. Vitatron Collection II Cardiac Pacemaker Pulse Generators	9/99	No[3]	No, OPCs and historical controls used
4. Sofamor Danek Interfix Threaded Fusion Device	5/14/99	Yes	Yes, Initial RCT design was ultimately abandoned because of problems in patient recruitment
5. Kappa 700/600 Cardiac Pacemaker Pulse Generator	1/29/99	No[4]	No, OPCs and historical controls used
6. Gem DR Implantable Cardiac Defibrillator	10/9/98	No[5]	No, OPCs and historical controls used
7. Kappa 400 Cardiac Pacemaker Pulse Generator	1/30/98	No[6]	No, OPCs and historical controls used
8. AVE Micro Stent II Coronary Stent	12/23/97	Yes[7]	Yes, market approved stent used as a control
9. Freestyle Prosthetic Heart Valve	11/26/97	No	No, OPCs used
10. InterStim Sacral Nerve stimulation	9/29/97	Yes[8]	Yes

DEVICE	APPROVAL	BREAKTHROUGH?	RCT DESIGN?
11. Activa Tremor Control System	7/31/97	Yes[9]	Yes[10]
12. Wiktor Prime Coronary Stent	6/27/99	Yes[11]	No, registry study
13. Legend Plus Cardiac Pacemaker Pulse Generator	2/7/99	No[12]	Yes, randomized comparison of rate responsive sensor modes

1 Includes PMAs initiated by Sofamor Danek and AVE prior to their merger with Medtronic.

2 OPC (Objective Performance Criteria)-based clinical trial design for prosthetic heart valves are based on guidance developed collaboratively between ODE, industry, and medical professionals.

3 First PMA approval for Vitatron pacemakers. Vitatron is a subsidiary of Medtronic located in The Netherlands.

4 Original PMA required for new rate responsive sensors; this is an evolutionary extension of pacemaker technology.

5 Original PMA required for the first dual chamber pacemaker with two rate responsive sensors; this is an evolutionary extension of pacemaker technology.

6 Medtronic's first ICD with dual chamber sensing and pacing capabilities; this is an evolutionary extension of ICD design.

7 AVE's first coronary stent approval received at a time when coronary stent application was still new.

8 Major new device therapy for treatment of urinary urge incontinence.

9 Major new device therapy for treatment of movement disorders.

10 Randomized comparison of the effects of electrical stimulation off and on for the relief of tremor.

11 Medtronic's first coronary stent approval received at a time when coronary stent application was still new.

12 Original PMA required for the first pacemaker with two rate responsive sensors; this is an evolutionary extension of pacemaker technology.

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